REMARKS

Status of the Claims

Claims 64, 65, 68-75, 91-103, 132-135, 140-143 and 146-165 are pending.

Claims 76-90, 136-139 and 144 had been withdrawn from consideration. Claims 71 and 73 were rejoined for examination. Claims 76-90, 136-139 and 144 remain withdrawn from consideration.

Claims 64, 65, 68-75, 91-103, 132-135, 140-143 and 146-165 have been rejected.

Upon entry of this amendment, claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 147-148 and 150-174 will be pending.

Summary of the Amendment

Applicants acknowledge that the Examiner has rejoined claims 71 and 73 for examination. Applicants have canceled claims 71, 73 and, 133-135, 140-143, 146, and 149 without prejudice to their presentation in another application. Applicants have amended claims 64 and 65 as described below. Claim 65 has also been amended to replace the term "induce" with the term "inhibit." Claims 166-174 have been added. Support for these amendments can be found throughout the specification and the claims as-filed and is discussed below.

The paragraph numbers discussed herein, refer to the numbering in the corresponding published application, which is US 2004/0258687 A1.

Claims 64 and 65 refer to a methods of inducing a cytostatic effect in a primary or metastasized colorectal, gastric or esophageal cancer cell and inhibiting the proliferation of a primary or metastasized colorectal, gastric or esophageal cancer cell, respectively, in an individual. The methods claimed in claims 64 and 65 both comprise administering into the circulatory system of an individual, a cytostatically effective amount of a guanylyl cyclase C ligand sufficient to have a therapeutic effect. The cytostatically effective amount of a guanylyl cyclase C ligand is stated as an amount sufficient to maintain a concentration $\geq EC_{50}$ of the guanylyl cyclase C ligand for at least 15 days. Support for the amendments to claims 64 and 65 can be found throughout the specification and the as-filed claims.

For example, at ¶ 127, the specification states that the ligand can be "administered into the circulatory system." Additionally, the specification states at ¶ 128 that the ligand can be administered at a "sufficient level" to "maintain the concentration of the ligand." to achieve a the desired effect. The specification also discusses various doses, concentrations, and time durations with respect to the level that is maintained to achieve the desired effect. For example, at ¶ 177 the specification describes an administration of a dose that is sufficient for the concentration of the ligand to "stay at or above the EC_{50}." The specification describes maintaining the effective amount for various amounts of times, such as 20 hours. For example, at ¶ 128 the specification states that the ligand "must be present at a sufficient level for a sustained amount of time" to achieve the desired effect on the cells. Claims 64, 65, and 167-169 recite that a concentration is maintained for at least 15 days and/or 30 days. Support for these claims can be found where the specification describes various "Dosage Regimens" at ¶ 169-171. Under the heading of "Dosage regimens" the specification describes regimens that lasts for at least 15 and 30 days. Claim 166 states that the ligand is infused into the individual for at least 6 hours. Support for this claim can be found, for example, in the as-filed claims. Claims 171 and 172 recite methods that comprises the sequential administration, as opposed to simultaneous administration, of the ligand and a different therapeutic agent. That is, the ligand is administered prior to the administration of a different therapeutic agent. Support for these claims can be found, for example, at ¶ 18 where the specification describes that the methods of the claims can be "followed by" another step of administering a different therapeutic agent. With respect to new claim 176, the specification also states that the concentration can be maintained at an amount that is greater than or equal to ten times the EC_{50}. (Specification, ¶ 180 and 190). The remaining new claims not specifically referred to are supported throughout the specification and the claims as-filed.

No new matter has been added.

Supplemental Information Disclosure Statement

Applicants include herewith a supplemental information disclosure statement and the payment of any appropriate fee in connection with the filing of the information disclosure statement.

Rejections under 35 U.S.C. § 112, first paragraph

Enablement

Claims 65, 68-75, 91-103, 145, and 147-165 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. Applicants have amended claim 65 to replace the term "induce" with the term "inhibit." Inclusion of the term induce was a typographical error as reflected in the preamble of the claim and the description throughout the specification. Applicants respectfully assert that the claims are enabled because the specification teaches one of skill in the art how to inhibit proliferation of cells without undue experimentation.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph alleging that the claims are not enabled be withdrawn.

Rejections under 35 U.S.C. 112, second paragraph

Claim 149 stands rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 149 was rejected under 35 U.S.C. § 112, second paragraph because it recites "the method of claim" without referring to the claim from which it depends. Applicants inadvertently omitted the claim from which claim 149 depended from. However, applicants have cancelled claim 149 rendering the rejection moot.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejections under 35 U.S.C. 112, first paragraph

Written Description

Claims 65, 68-72, 74, 75, 91-103, 145, and 147-165 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Claim 65 has been amended to replace the term "induce" with the term "inhibit." One of skill in the art would clearly understand that Applicants were in possession of the amended claim at the time the present application was filed.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph for allegedly failing to satisfy the written description requirement be withdrawn.

Rejections under 35 USC § 102

Claims 64 and 68-74 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,879,656 as evidenced by Shilubhai *et al.* (Cancer Research, Sep. 15, 2000 60:5151-5157). The Office alleges the '656 patent discloses the elements of the claims. Applicants respectfully disagree.

Applicants respectfully disagree that the '656 patent anticipates the claims, but in order to further prosecution Applicants have amended claim 64 to further clarify the claim. Claim 64 as amended states, in part, that the ligand is administered into the circulatory system of an individual and the amount is a cytostatically effective amount of a guanylyl cyclase C ligand sufficient to have a therapeutic effect, wherein the cytostatically effective amount of a guanylyl cyclase C ligand is an amount sufficient to maintain a concentration $\geq EC_{50}$ of said guanylyl cyclase C ligand for at least 15 days. The '656 patent fails to disclose or suggest a ligand that is administered into the circulatory system of an individual and the amount is a cytostatically effective amount of a guanylyl cyclase C ligand sufficient to have a therapeutic effect, wherein the cytostatically effective amount of a guanylyl cyclase C ligand is an amount sufficient to maintain a concentration $\geq EC_{50}$ of said guanylyl cyclase C ligand for at least 15 days. For a

reference to anticipate a claimed invention the reference must disclose each and every limitation either explicitly or inherently. Therefore, because the '656 patent fails to disclose each and every element of the pending claims the '656 patent fails to anticipate the claims.

The '656 patent also fails to anticipate new claims 166-174 because the '656 patent does not disclose each and every element of the claims.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Rejections under 35 USC § 103

Claims 75, 91-103, 132-135, 140-143 and 145-165 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,879,656, in view of Cohen (Int J. Radiat Oncol Biol Phys, 1987, 13:251-8), in further view of U.S. Patent No. 6,251,439, in further view of Harlow and Lane (Antibodies, a Laboratory Manual, Cold Spring Harbor Laboratory Press, 1988, p. 141-142), in further view of Queen *et al.* (PNAS, 1989 86:10029-10033) and in further view of Riechmann *et al* (Nature 1988 332:323-327). Applicants respectfully disagree.

The pending claims are not obvious because the Office has failed to support a conclusion that the pending claims are *prima facie* obvious. M.P.E.P. § 2141 states that the "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." "[T]his analysis should be made explicit" and it "can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). The Office has failed to articulate a sufficient reason why one of skill in the art would have been led to the pending claims. The cited references fail to teach or suggest administering a cytostatically effective amount of a guanylyl cyclase C ligand into the circulatory system with a cytostatically effective amount of a guanylyl cyclase C ligand sufficient to have a therapeutic effect, wherein the cytostatically effective amount of a guanylyl

cyclase C ligand is an amount sufficient to maintain a concentration $\geq EC_{50}$ of said guanylyl cyclase C ligand for at least 15 days.

New claims 166-174 are also not obvious because the references cited by the Office do not yield the claimed invention. Claims 166-174 are directed to other embodiments of the claimed methods. For example, none of the references cited by the Office, alone or in combination, discuss sequential administration of a ligand followed by a different therapeutic agent. Therefore, claims 166-174 are also not obvious in view of the cited references.

Accordingly, the claims are not obvious because either the Office has failed to support *a prima facie* case of obviousness because there is no suggestion to modify or combine the references and even if combined the combination of the references fails to yield the claimed invention. In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Double Patenting

Claims 64, 68-73, 91-102, 132, 133, 135, 140-143 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 10, 11, 15-28, 33, and 36-39 of copending Application No. 11/166,952 in view of Cohen (Int J. Radiat Oncol Biol Phys, 1987, 13:251-8) and in further view of U.S. Patent No. 5,879,656. Applicants respectfully disagree.

Claims 64, 68-75, 91-102, 132-135, 140-143, 145, and 146 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 30-32, 35-38, 40-55, and 57-65 of copending Application No. 10/866,951 in view of Cohen (Int J. Radiat Oncol Biol Phys, 1987, 13:251-8), in further view of Queen *et al.* (PNAS, 1989 86:10029-10033) and in further view of Riechmann *et al* (Nature 1988 332:323-327). Applicants respectfully disagree.

The grounds of nonstatutory obviousness-type double patenting are based upon the allowed claims. The present application, the '951 application, or the '952 application have not

been indicated to have allowed claims. Therefore, Applicants respectfully request that the rejection under the nonstatutory obviousness-type double patenting at this time is improper. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Conclusion

Claims 64, 65, 68-70, 72, 74, 75, 91-103, 132, 147-148 and 150-174 are in condition for allowance. A notice of allowance is earnestly solicited.

The Commissioner is hereby authorized to charge any deficiencies of fees and credit of any overpayments to Deposit Account No. 50-0436.

Respectfully submitted,

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